Head and neck

Oral tongue carcinoma: prognostic changes according to the updated 2020 version of the AJCC/UICC TNM staging system

Il carcinoma della lingua mobile: i cambiamenti della prognosi in base alla versione 2020 del sistema di classificazione AJCC/UICC TNM

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SUMMARY

Background. This study aimed to evaluate the performance of the 2017 8th TNM edition and the latest update in 2020 compared to the 7th in a large cohort of patients affected by oral tongue squamous cell carcinoma (OTSCC), considering all stages.
Materials and methods. The cohort involved 300 patients affected by OTSCC treated with surgery. All cases were classified according to the 7th, 8th (2017), and the latest updated TNM edition (October 2020),. Patients were grouped based on the shift in tumour (T) category, lymph nodal (N) category and final pathological stage. Overall survival (OS) and disease-free survival (DFS) were calculated with the Kaplan-Meier method. Univariate and multivariate analyses were carried out.
Results. According to the 7th edition, multivariate analysis OS revealed that stage IV patients had an almost 4-fold risk of death compared to stage I (HR = 3.81 95% CI: 2.32-6.25; p < 0.001). Regarding DFS, stage IV patients had a 2-fold greater risk of relapses, or second primary, than patients in stage I (HR = 2.51 95% CI: 1.68-3.74; p < 0.001). According to 2017 8th edition for OS, stage IV patients presented a 5-fold higher risk of death compared to patients in stage I (HR = 5.18 95% CI: 2.96-9.08; p < 0.001) and almost 4-old greater risk of relapses or second primary compared to patients in stage I considering DFS (HR = 3.61 95% CI: 2.28-5.71; p < 0.001). Regarding the recent edition of 8th TNM (2020), stage IV patients had an almost 5-fold greater risk of death compared to patients in stage I considering OS (HR = 4.84 95% CI: 2.74-8.55; p < 0.001), while for DFS they had 3-fold greater risk of relapse or second primary compared to patients in stage I (HR = 3.13 95% CI: 1.99-4.91; p < 0.001).
Conclusions. This study confirmed that the recent update of the 8th edition of the TNM (2020) improves stratification and identification of advanced tumours, reducing the number of T3 compared to the 2017 edition and increasing the number of patients with pT4. This improvement made by the updated edition may reduce the risk of skipping adjuvant therapy.

KEY WORDS: tongue cancer, TNM, depth of invasion (DOI), prognosis, survival, stage migration

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RIASSUNTO

Obiettivo. Questo studio mira alla valutazione dell'efficacia predittiva dell'8ª edizione del TNM (2017) e dell'ultima versione aggiornata nel 2020 rispetto alla 7ª applicandole in un'ampia coorte di pazienti affetti da carcinoma spinocellulare della lingua mobile, considerando tutti gli stadi.
Metodi. Il gruppo di studio consta di 300 pazienti affetti da carcinoma spinocellulare della lingua mobile trattati chirurgicamente. Tutti i casi sono stati classificati in base alla 7ª, 8ª (2017) e all'aggiornata (ottobre 2020) edizione del TNM. I pazienti sono stati raggruppati

in base alla migrazione della categoria del tumore (T), dello stato linfonodale (N) e dello stadio patologico finale. La sopravvivenza globale (OS) e la sopravvivenza libera da malattia (DFS) sono state calcolate con il metodo Kaplan-Meier. Sono state effettuate analisi univariate e multivariate.

Risultati. Secondo la 7ᵃ edizione, l'analisi multivariata della OS mostra che i pazienti in stadio IV hanno un rischio di morte quasi quadruplo rispetto a quelli in stadio I (HR = 3,81 IC 95%: 2,32-6,25; p < 0,001). Per quanto riguarda la DFS, i pazienti in stadio IV hanno un rischio due volte maggiore di recidive, rispetto ai pazienti in stadio I (HR = 2,51 IC 95%: 1,68-3,74; p < 0,001). Secondo l'8ᵃ edizione del 2017, per quanto riguarda l'OS i pazienti in stadio IV hanno un rischio di morte cinque volte superiore rispetto ai pazienti in stadio I (HR = 5,18 IC 95%: 2,96-9,08; p < 0,001) e un rischio quasi quattro volte maggiore di recidiva o secondo tumore rispetto ai pazienti in stadio I considerando la DFS (HR = 3,61 IC 95%: 2,28-5,71; p < 0,001). Per quanto riguarda la recente edizione dell'8ᵃ TNM (2020), i pazienti in stadio IV presentano un rischio di morte quasi cinque volte maggiore rispetto ai pazienti in stadio I considerando OS (HR = 4,84 IC 95%: 2,74-8,55; p < 0,001), mentre riguardo alla DFS, presentano un rischio tre volte più elevato di sviluppare recidive o secondi tumori rispetto ai pazienti in stadio I (HR = 3,13 IC 95%: 1,99-4,91; p < 0,001).

Conclusioni. Questo studio ha confermato che il recente aggiornamento dell'8ᵃ edizione del TNM (2020) migliora la stratificazione e l'identificazione dei tumori in stadio avanzato, in particolare riducendo la numerosità dei T3 rispetto all'edizione 2017 e aumentando quella dei pT4. In questo modo, si riduce la possibilità di non eseguire la terapia adiuvante a causa della diversa stadiazione del TNM.

PAROLE CHIAVE: *carcinoma della lingua, TNM, profondità d'invasione (DOI), prognosi, sopravvivenza, migrazione di stadio*

Introduction

Oral tongue squamous cell carcinoma (OTSCC) is the most common neoplasia of the oral cavity [1,2], accounting for about 25-40% of all oral malignancies [3] with a 5-year overall survival (OS) and disease-free survival (DFS) of about 50% and 60%, respectively [3,4]. OTSCC generally stands out by a high rate of lymphatic neck metastasis, a high risk of local recurrence and the possibility to develop drug resistance to chemotherapy during systemic treatment [4,5].

Even if tumour depth of invasion (DOI) – defined as the distance between the level of the basement membrane of the closet adjacent normal mucosa and the deepest point of tumour invasion [6] – was already associated with an increased risk of lymph node metastasis [7], it was not included in the 7th edition of the staging system for oral squamous cell carcinoma (SCC) [8].

In 2017, the new 8th TNM edition of the AJCC/UICC staging system introduced DOI in oral tumour classification and added extranodal extension (ENE) to the lymph node category (N) in the pathological and clinical stage as negative prognostic factors. Therefore, primary tumours categorised as T1 according to the 7th edition were upstaged to T2 in the presence of a 5 mm invasion beyond the basement membrane. Primary tumours formerly categorised as T2, or even T1, were upstaged to T3 if DOI > 10 mm.

Additionally, on 6th October 2020, the AJCC/UICC staging system published an erratum edition of TNM, updating the definition of T4 for oral cavity cancer [9]. Despite the previous classification, pT4a oral cavity cancer was defined as a tumour > 4 cm in greatest dimension, and > 10 mm DOI or those invading through the cortical bone of the mandible, maxilla, maxillary sinus or skin of the face. The new tridimensional criteria in terms of maximum diameter and deep infiltration helped distinguish T3 from T4a tumours [9].

Concerning lymph node category, the 8th TNM edition included ENE, defined as the extension of metastatic carcinoma from within a lymph node through the fibrous capsule and into the surrounding connective tissue [10]. In detail, the extranodal extension < 3 cm in diameter in a single node is staged as pN2a, and all other cases with ENE (ENE+) are classified as pN3b [10-12].

The purpose of this study, comparing the three versions of TNM, was to evaluate the performance of recent editions (2020) of the AJCC Cancer Staging Manual to understand how it improves oral tongue cancer staging considering the main prognostic factors (ENE, DOI, tumour diameter) and how it may better define and stratify prognosis.

Materials and methods

This is a retrospective cohort of 300 consecutive patients affected by oral tongue squamous cell carcinoma (OTSCC) treated with surgery and adjuvant therapy at the Division of Otorhinolaryngology and Head and Neck Surgery of the European Institute of Oncology, IRCCS (IEO) from January 2010 to December 2017.

Inclusion criteria was newly diagnosed with mobile tongue squamous cell carcinoma treated with surgery followed by adjuvant therapy based on histopathological findings and all stages according to AJCC 7th edition.

We excluded pre-treated patients (prior surgery, radiotherapy, radio-chemotherapy), other histotypes than SCC, and the presence of distant metastasis at diagnosis.

According to the good clinical practice guideline, all useful variables and study data were collected and analysed in a specifically-designed database.

Histopathological features collected: grading (G1-3), maximum tumour diameter (T) (mm), tumour infiltration (DOI) (mm), multifocality, vascular (LVI) and perineural infiltration (PNI), intrinsic and extrinsic tongue muscle involvement, status of surgical margins, total number and pathological lymph nodes removed, presence of ENE or lymph node micro-metastases, T-N tract status (free or involved by disease) [13]. Based on the 7th pathological (c) TNM edition, we reported the clinical tumour stage. Each case of OTSCC was re-studied according to the 8th TNM edition 2017 [11] and the recent errata version (2020) of the TNM staging system [9]. All cases without data on DOI were reviewed by a head and neck pathologist (FAM) according to the current definition of DOI [14]. Patients with involvement of extrinsic tongue musculature by disease were considered with a DOI greater at least than 10 mm [15].

We also described postoperative adjuvant therapies (radio-therapy or radio-chemotherapy) performed according to the 7th pathological stage TNM.

All patient follow-ups were reported and updated to assess their status at the last follow-up date.

We analysed the trend of each stage and T category migration according to each type of TNM system staging.

To evaluate the possible impact of the two last TNM editions on survival rates, we performed OS and DFS analysis comparing the equal-, up- and down-staged categories. The agreement between the clinical tumour staging (cTNM) and pathological tumour staging (pTNM) 7th edition was also evaluated.

Statistical analysis

Clinical characteristics were compared using the Pearson Chi-square test for categorical variables and Wilcoxon rank test for continuous variables. All survival curves were constructed using the Kaplan-Meier method and compared by log-rank test.

Overall survival (OS) was defined as the time from surgery to the patient's death for any cause or the last available follow-up. Disease-free survival (DFS) was defined as the time from surgery to the progression of the disease, second primary, death from any cause, or the last available follow-up. We compared 5-year OS and DFS. The prognostic value of the TNM stage in the three editions was evaluated by Cox proportional hazard models adjusting for age. For all tests, the significance level was set at $p < 0.05$. All analyses were performed using the software R ver. 3.6.0 - "Planting of a Tree" (R Core Team 2019) [16].

Results

The study included 300 patients, and demographic-clinical features are summarised in Table I. There were 170 males

Table I. Clinical and histopathological characteristics of the cohort (n = 300).

Variables	n (%)
Median age (IQR)	59 years (70.25-46)
Sex	
M	170 (57)
F	130 (43)
Smoking	
No	114 (38)
Yes	107 (36)
Ex-former	76 (25)
Pack/year	29
Alcohol habits	
No	198 (66)
Yes	81 (27)
Ex former	11 (4)
Former	6 (2)
Drinks/day	4
Tongue tumour site	
Margin	238 (79)
Body/dorsum	27 (9)
Ventral tongue	23 (8)
Posterior third	12 (4)
Adjuvant therapy	
RT	87 (29)
CRT	56 (19)
Median follow-up	53 months
Follow-up status	
NED	177 (59)
AWD	15 (5)
DOD	80 (27)
DOC	28 (9)
Site of recurrence	99 (33.0)
T	13 (13)
N	46 (47)
Loco-regional (T+N)	7 (7)
Loco-regional and distant (T/N + M)	11 (11)
Metastasis	22 (22)
Second tumour	12 (4)
Head and neck cancer	7 (58)
No head and neck cancer	5 (42)
Grading	
G1	62 (20)
G2	138 (46)
G3	67 (22)
Missing	33 (11)
Micro-metastasis	
No	293 (98)

▶

Table I. Clinical and histopathological characteristics of the cohort (n = 300) *(follows).*

Variables	n (%)
Yes	7 (2)
Multifocality	
No	293 (98)
Yes	7 (2)
Margin status	
Free	268 (89)
Positive	20 (7)
Close (< 1 mm)	12 (4)
Vascular infiltration	
No	282 (94)
Yes	18 (6)
Intrinsic muscle infiltration	
No	57 (19)
Yes	243 (81)
Extrinsic muscle infiltration	
No	144 (48)
Yes	156 (52)
T-N status	
Not removed	139 (46)
Free from disease	117 (39)
Involved by disease	44 (15)
ECE	
No	231 (77)
Yes	69 (23)

RT: radiotherapy; CRT: chemo-radiotherapy; NED: Non-Evidence of Disease; AWD: Alive with Disease; DOD: Dead of Disease; DOC: Dead of Other Causes; T: tumour; N: nodal status; ECE: extracapsular extension; IQR: Interquartile range.

(57%). Median age was 59 years (interquartile range [IQR]: 70.25-46). The lingual margin was the most frequent subsite involved by cancer (79%). The histopathological features of our sample are summarised in Table I.

Regarding postoperative therapies: overall, 143 patients (48%) underwent adjuvant therapy; 87 cases underwent adjuvant radiotherapy (29%), while 56 patients (19%) needed radio-chemotherapy. Beyond the stage, the risk factors considered to perform the adjuvant radiotherapy were extrinsic muscles involved by the tumour (52%), vascular invasion (6%), T-N tract involved by cancer (15%) and positive or close margins (11%). Radio-chemotherapy was reserved for ECE+ patients (23%) (Tab. I).

The median follow-up was 53 months. At last follow-up, 177 (59%) were alive with no evidence of disease (NED), and 15 (5%) were alive with disease (AWD). Eighty patients (27%) died because of tongue cancer disease (DOD), and 28 (9%) died for other causes (DOC) (Tab. I).

Migration stage

Clinical and pathological TNM according to 7th, 8th (2017), and recently updated version (2020) of TNM edition are reported by Figure 1. No staging change occurred in 67% of cases (n = 200), while 8% (n = 23) of cases were up-staged and 22% (n = 65) were down-staged, according to the 2017 8th TNM edition staging system.

Comparing the 7th and the 2020 8th edition, no change in staging occurred in 71% of cases (n = 213), while 9% (n = 27) of cases were up-staged and 16% (n = 48) were
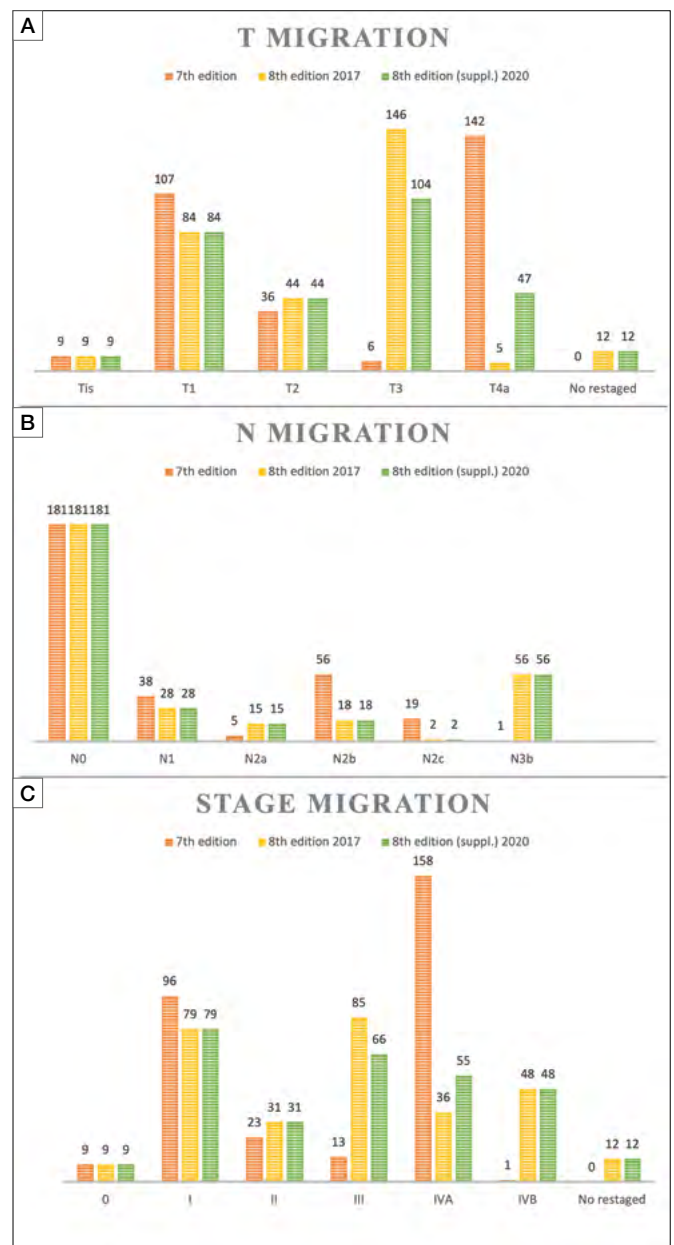
Figure 1. Migration of the pathological system staging of T (**a**), N (**b**) and stage (**c**) according to 7th, 8th and the updated 8th edition.

down-staged. Considering stages I and II, the change was the same for each 8th edition (2017 and 2020). Among 96 patients staged previously as stage I (7th edition), 4 cases became stage III, 13 cases stage II and 79 cases remained stage I.

In addition, of 23 cases previously staged as II (7th edition), 5 cases became stage III and the remaining 18 cases stage II.

For stages III and IVa, the application of the recently updated version of TNM (2020) showed a different migration compared to the 8th 2017 version.

Among 12 cases previously staged as stage III (7th edition), 1 case became stage IVa according to the 8th TNM 2017 edition, while applying the updated version (2020) 3 cases became stage IVa.

Moreover, of 147 cases previously staged as IVa (7th edition), 65 cases became stage III and 47 cases became stage IVb based on the 2017 8th TNM edition. Applying the 2020 TNM on 147 cases previously staged as IVa (7th edition), 48 cases became III, 47 became stage IVb, and 52 patients remained IVa.

Survival curves

OS at 3 (OS-3yrs) and five years (OS-5yrs) was 70% and 60%, respectively. DFS at 3 (DFS-3yrs) and five years (DFS-5yrs) was 60% and 50%, respectively (data not shown).

Survival analysis 7th TNM edition

Figure 1a shows OS-5yrs related to the 7th TNM edition: 80% for stage 0-I, 75% for stage II, 85% for stage III and 48% for stage IV (p < 0.01).

DFS-5yrs was 65% for stage 0-I, 55% for stage II, 60% for stage III and 47% for stage IV, (p < 0.01) (Fig. 1b).

Multivariate analysis revealed that stage IV patients had an almost 4-fold risk of death (OS) compared to stage I (HR = 3.81 95% CI: 2.32-6.25; p < 0.001). Stage IV patients had more than twice the risk of events (DFS) compared to patients in stage I (HR = 2.51 95% CI: 1.68-3.74; p < 0.001) (Tab. II).

Survival analysis 8th TNM edition, 2017

For the 8th TNM 2017 edition of the staging system, OS-

Table II. Multivariate analysis using Cox regression.

			HR	Low 95% CI	Up 95% CI	P-value
TNM 7th	DFS	Stage II *vs* stage I	**1.08**	**0.48**	**2.44**	**0.855**
		Stage III *vs* stage I	1.22	0.43	3.45	0.707
		Stage IV *vs* stage I	2.51	1.68	3.74	**< 0.001**
		Age	1.02	1.01	1.03	**< 0.001**
	OS	Stage II *vs* stage I	0.66	0.20	2.23	0.504
		Stage III *vs* stage I	1.07	0.25	4.58	0.93
		Stage IV *vs* stage I	3.81	2.32	6.25	**< 0.001**
		Age	1.03	1.01	1.04	**< 0.001**
TNM 8th	DFS	Stage II *vs* stage I	1.12	0.56	2.26	0.742
		Stage III *vs* stage I	1.50	0.91	2.48	0.110
		Stage IV *vs* stage I	3.61	2.28	5.71	**< 0.001**
		Age	1.02	1.01	1.03	**< 0.001**
	OS	Stage II *vs* stage I	0.86	0.34	2.20	0.761
		Stage III *vs* stage I	2.18	1.19	3.98	0.011
		Stage IV *vs* stage I	5.18	2.96	9.08	**< 0.001**
		Age	1.03	1.01	1.04	**< 0.001**
TNM 8th (suppl.)	DFS	Stage II *vs* stage I	0.97	0.47	2.02	0.93
		Stage III *vs* stage I	1.26	0.72	2.18	0.42
		Stage IV *vs* stage I	3.13	1.99	4.91	**< 0.001**
		Age	1.02	1.01	1.03	**0.001**
	OS	Stage II *vs* stage I	0.89	0.34	2.30	0.805
		Stage III *vs* stage I	1.73	0.88	3.42	0.11
		Stage IV *vs* stage I	4.84	2.74	8.55	**< 0.001**
		Age	1.03	1.01	1.04	**< 0.001**

5yrs was 80% for stage 0-I, 78% for stage II, 65% for stage III and 40% for stage IV (p < 0.01) (Fig. 1c).

DFS-5yrs was 70% for stages 0-I, 62% for stage II, 55% for stage III and 45% for stage IV (p < 0.01) (Fig. 1d).

Multivariate analysis for OS stage IV patients revealed a 5-fold greater risk of death compared to patients in stage I (HR = 5.18 95% CI: 2.96-9.08; p < 0.001), and almost 4-fold greater risk of events compared to patients in stage I considering DFS (HR = 3.61 95% CI: 2.28-5.71; p < 0.001).

Survival analysis 8th TNM edition, 2020

Concerning the update 8th TNM version (2020), OS-5yrs was 80% for stage 0-I, 78% for stage II, 70% for stage III, and 40% for stage IV (p < 0.01) (Fig. 1e).

DFS-5yrs was 74% for stages 0-I, 72% for stage II, 60% for stage III and 32% for stage IV (p < 0.01) (Fig. 1f).

OS stage IV patients had an almost 5-fold greater risk of death compared to patients in stage I considering OS (HR = 4.84 95% CI: 2.74-8.55; p < 0.001) and, considering DFS, a 3-fold greater risk of events compared to patients in stage I (HR = 3.13 95% CI: 1.99-4.91; p < 0.001) in multivariate analysis.

Comparing the 7th with the 2017 TNM edition 5-yr OS and 5-yr DFS, we observed that up-staged 5-yr OS was worse, while in the case of down-staged patients 5-yr OS was improved (p < 0.001) (Fig. 3).

There were no significant differences in OS or DFS comparing 7th ed. with the updated TNM (2020) (p = 0.10 and p = 0.06 respectively) (Fig. 2).

Finally, older age in multivariate analysis was confirmed as an independent negative prognostic factor for survival (OS and DFS), considering each TNM staging (p < 0.001) (Tab. II).

Changes in tumour (T) and lymph nodal status (N) classification

Focusing on the tumour (T) category, 107 cases defined as pT1 (7th edition) were up-staged to pT2 and pT3, respectively, in 18 and 5 cases, while 84 patients were equal-staged as pT1, based on both 8th editions of TNM.

Nine cases of 35 defined as pT2 were up-staged to pT3, while 26 patients were equal-staged as pT2, based on both two 8th editions of TNM.

Among 142 pT4a (7th TNM), 128 and 88 patients were down-staged to pT3 based on the previous and recent 8th edition. In addition, 5 and 45 patients were equal-staged as pT4a, based on the previous and recent 8th editions, respectively.

According to lymph nodal status (N), the "migration" observed was: 10 patients with pN1 in the 7th edition became pN2a in the 8th (2017 and 2020), and 26 patients remained as pN1.

Among 56 pN2b, 40 cases became pN3b, and 18 remained pN2b. Nineteen patients were pN2c according to the 7th edition: 17 became pN3b, 2 remained pN2c, and one pN3 remained pN3b according to the 8th edition TNM staging system.

Survival analysis - tumour (T) classification

Concerning 5-yr OS, we observed no differences on T1, T2, T3 and T4 category according to each type of TNM system staging (respectively: p = 0.83, p = 0.95, p = 0.60, p = 0.13) (data not shown).

In the same way, no significant differences were found for 5-yr DFS on T1, T2, T3 and T4 category according to each type of TNM system staging (respectively: p = 0.95, p = 0.87, p = 0.75, p = 0.22) (data not shown).

Changing in postoperative treatments according to the new TNM staging

Focusing on adjuvant therapy for stage IVa (158 patients, 7th edition): 80 patients underwent radiotherapy and 49 underwent radio-chemotherapy. Considering this group (158 IVa stage patients, 7th edition), 65 cases were down-staged according to the 2017 8th edition, and among those, 33% (n = 53) underwent radiotherapy, while one patient received radio-chemotherapy due to ECE+. Equal-staged occurred in 35 cases, 12 patients (8%) received radio-chemotherapy, and 17 (11%) radiotherapy.

According to the 2020 8th TNM, among 48 down-staged to stage III, one patient received radio-chemotherapy, and 40 (25%) patients received radiotherapy. Concerning patients up-staged according to the 2017 and 2020 8th editions, among 47 restaged as IVb, 10 patients (6%) underwent radiotherapy, while 36 (23%) patients received radio-chemotherapy. Equal-stage occurred in 52 cases, and 12 patients (8%) received radio-chemotherapy and 30 (19%) radiotherapy alone.

Considered the adjuvant therapy of stage III (12 cases according to 7th TNM edition): five patients underwent postoperative radiotherapy, of which 1 case was upstaged to IVa due to ECE+ in the 8th edition (2017 and 2020). The remaining 12 cases had risk factors for postoperative radiotherapy (T-N tract involved by disease, PNI and LVI).

Concerning the 2020 8th TNM, 3 cases were upstaged to IVa (stage III in the 7th edition) and underwent postoperative radiotherapy.

Clinical and pathological tumour stage agreement

The comparison between the clinical tumour staging (cTNM) and pathological tumour staging (pTNM) 7th edition
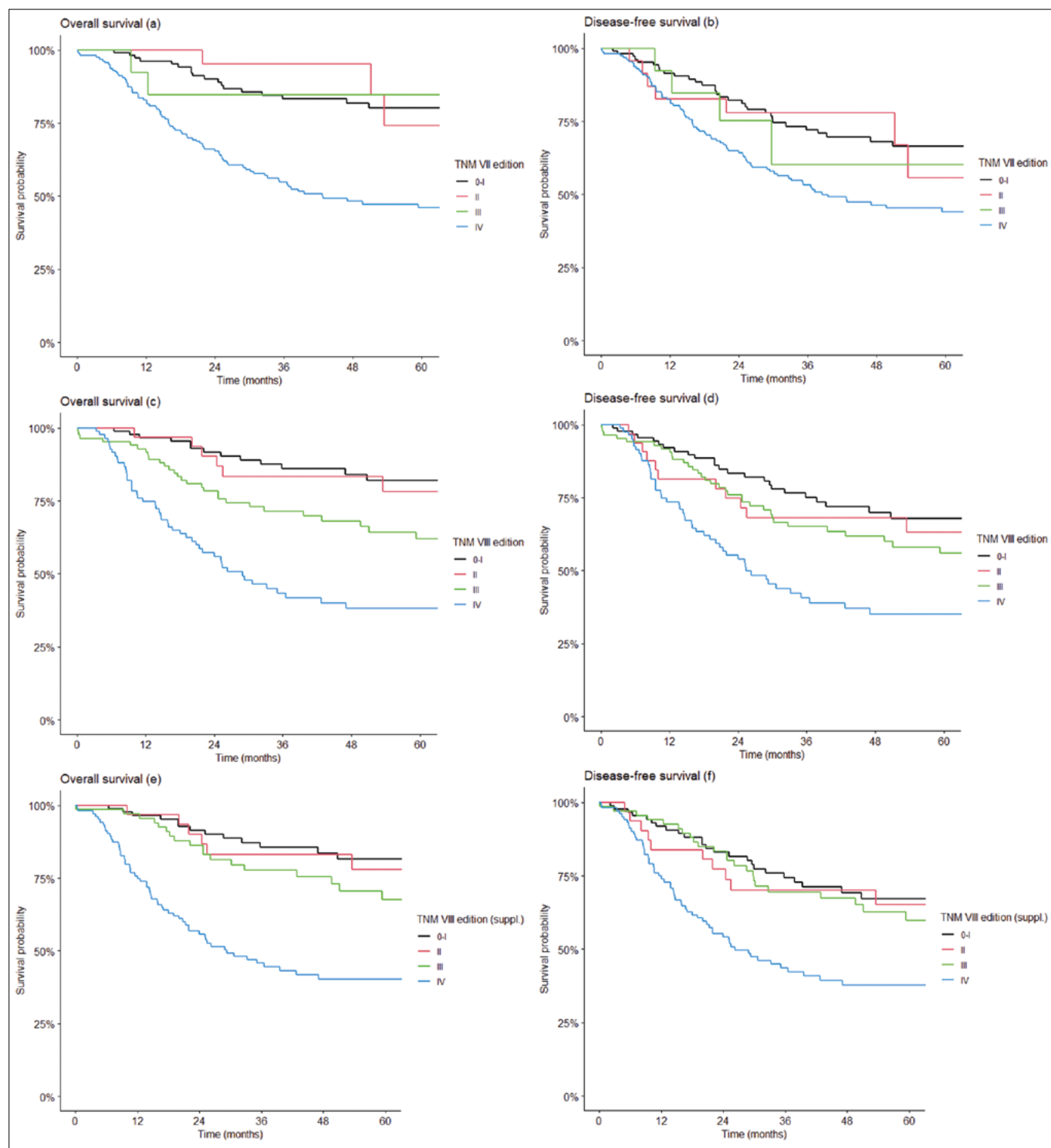
Figure 2. OS (**a**) and DFS (**b**) with the TNM 7th edition; OS (**c**) and DFS (**d**) with the previous TNM 8th edition; OS (**e**) and DFS (**f**) with the updated TNM 8th edition.

indicated good agreement, with a Cohen's kappa of 0.71 (95% confidence interval [95% CI]: 0.64-0.78) (data not shown). Whereas the comparison of clinical staging cTNM with pTNM based on the previous 8th edition indicated a fair agreement of about 36.5%, with a Cohen's kappa of 0.41 (95% CI: 0.21-0.30) (data not shown). The same evaluation with the updated (2020) 8th edition revealed an excellent agreement of 47.4% (95% CI: 0.27-0.39) (data not shown).
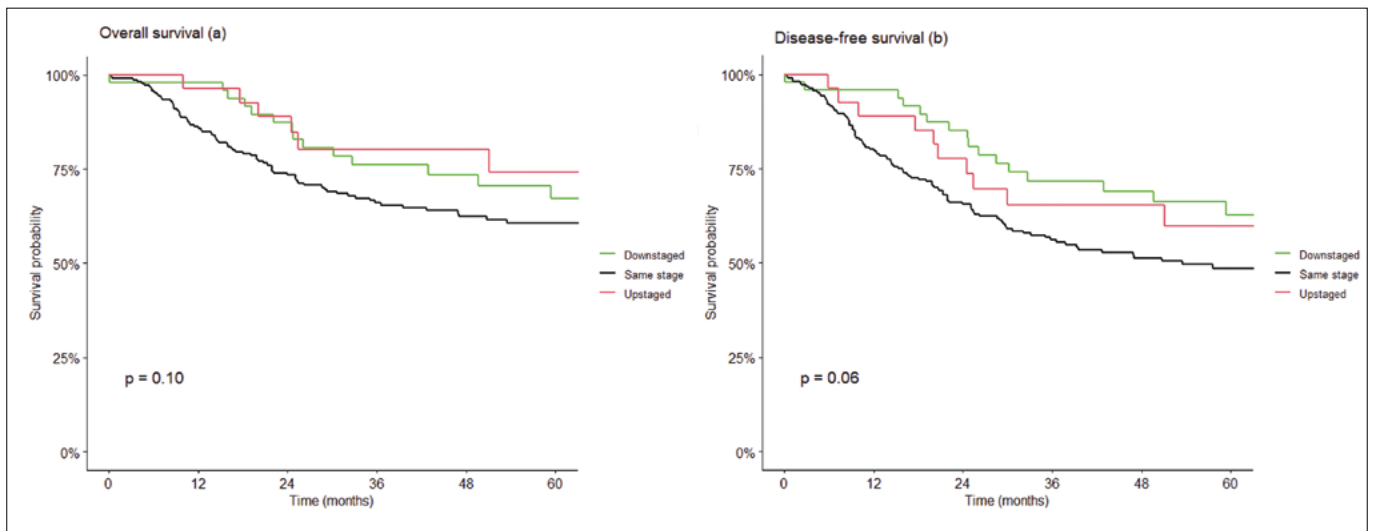
Figure 3. OS (**a**) and DFS (**b**) related to the change of stages between the 7th and 2020 8th TNM edition.
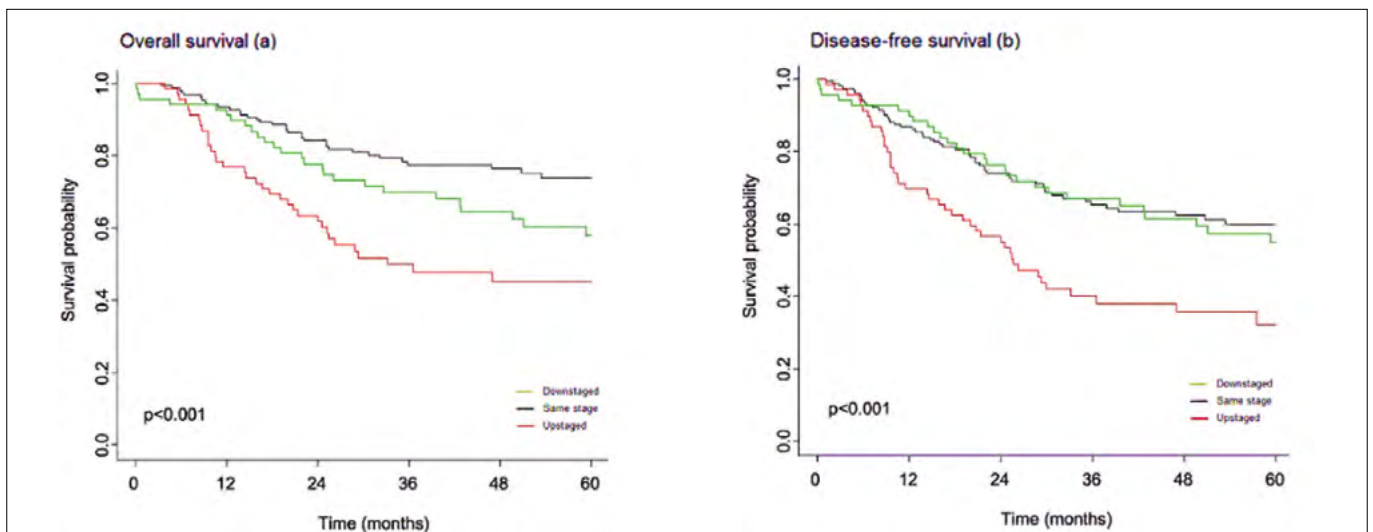

Figure 4. OS (**a**) and DFS (**b**) related to the change of stages between the 7th and 2017 8th TNM edition.

Discussion

This study on a large monocentric cohort (300 patients affected by mobile tongue SCC) investigated the performance of the 8th edition of the AJCC Cancer Staging Manual, considering the last two versions (2017-2020), compared with the 7th edition in terms of survival outcomes (OS and DFS). The most evident change concerns pT3 and pT4a: the 2017 8th TNM application led to a considerable increase of pT3 tumours. Conversely, the recent version of the 2020 TNM led to a more uniform re-distribution of stages pT3 and pT4a compared with the 2017 8th edition.

The main finding of this work is that the tumour group clas-

sified as T3 by the 7th edition was very small (6 patients). As already published [17], the 8th 2017 version led to a significant increase in tumours classified as T3: in our study, there were 146 patients according to this edition compared to only 6 in the 7th edition.

However, the changes made in the updated edition (2020) seems to balance these categories by redistributing the number of tumours classified as T3 and T4 and by rebalancing relative prognosis: in our cohort, 104 patients were re-classified as T3 and 47 patients as T4a (5 patients were T4a according to the 8th edition 2017).

Focusing on T survival rates (OS and DFS), we did not ob-

serve any relevant difference for either T1 or T2, according to the different TNM staging systems [18].

The 5-yr DFS of T3 and T4a, according to the updated 2020 version, was better than the 8th TNM 2017 edition. Hence, the stage III 5-yr OS was worse, according to the 2017 8th TNM edition. We did not find any difference between the two versions of the 8th TNM for stage IV: 5-yr OS was worse when considering the last two editions than the 7th TNM.

After analysis of survival rates in terms of DFS for the three TNM editions, we can assume that the 8th edition 5-yr DFS is better for stage II, while we registered a worsening of the 5-yr DFS for stage IV in the updated 2020 8th TNM. Nevertheless, in the 2017 8th TNM edition staging system, 5-yr DFS for stage III patients was worse, while with the updated 2020 edition it was similar to the 7th TNM edition. To better understand this survival trend, we analysed equal, up-and-down-staging cases. We observed that patients who changed stage showed better OS and DFS according to the 2017 and 2020 TNMs. Tirelli et al. reported that the 7th edition of the TNM classification seemed to fail prognosis prediction in patients with similar stages and treatments due to its unprecise potential of prognosis [19]. Furthermore, the 7th TNM edition underestimates 5-yr OS and 5-yr DFS in advanced stages (stage III and IV), with a worse prognosis according to the new 8th edition. This data confirms that the 2020 updated staging system improves survival perspectives due to better risk stratification.

According to the 2017 8th TNM, neoplasms that invade through the cortical bone of the mandible or maxilla, involve the maxillary sinus, or invade the skin of the face, were pT4a [11]. The updated 2020 TNM version defines pT4a as neoplasms with a maximum dimension > 4 cm and DOI > 10 mm, in addition to invasion of adjacent soft and bone tissues [9].

The inclusion of the tridimensional parameter to define the new pT4a and pT3 allows more precise and homogenous staging, overcoming the limitations of the previous TNM systems due to underestimation of pT3 with the 7th edition and pT4a with the 2017 8th TNM, without considering DOI and size of tumour.

The updated 8th TNM HR in DFS revealed midrange values between the 7th and the previous 8th TNM. These data reflect the effort of the updated TNM to more precisely predict prognosis for IVa stage through definition of pT3 and pT4a in terms of tumour size and DOI. According to the 8th TNM edition, OS for stage IV patients is burdened by a 5-fold greater risk of death compared to stage I, while, when considering the DFS, stage IV had a 3-fold higher risk of relapse, or second primary, compared to patients in stage I.

As is well known, DOI allows better discrimination between small oral cancers with limited superficial extension but which are deeply invasive. In contrast, those that are less invasive have better prognosis, independently of the external dimension [19].

Concerning postoperative therapies, all the upstaged cases by the 8th TNM edition could have been spared adjuvant therapies according to the 7th edition. Even in our experience, and following the 7th edition, advanced stages (IVa and IVb) underwent adjuvant therapies due to the presence of independent oncological risk factors (PNI, ECE+, LVI, N>1, pT3).

Moreover, all cases of tongue cancer involving the posterior third of the mobile tongue could have resulted down-staged and, consequently, avoided postoperative therapy, undergoing less aggressive surgery (transoral rather than major surgery). This is because the involvement of the posterior third of the mobile tongue generally corresponds to pT4a due to the invasion of hyoglossus muscle, according to the 7th TNM edition. At this level, the intrinsic muscles thickness is less than 1 cm. The extrinsic muscles are more easily infiltrated, and thus considering DOI, tumours involving the hyoglossus muscle can be now restaged as pT1 or pT2, according to the 8th edition.

The 8th edition has better re-defined the prognostic role of ECE, which remains the most important factor that influences the tumour's natural history and the patients' survival. Mattavelli et al. recently suggested that a single nodal metastasis with ENE was not significantly associated with poor prognosis compared to multiple ENE metastases [17]. In our study, according to ENE+, up-staging N occurred in 57 cases (20%) that were already treated with CRT for ECE, also according to the 7th edition. Nodal migration according to ECE did not cause a change in adjuvant treatment indications since it was a factor that was already considered.

Thus, the uniformity of indications for postoperative therapies did not seem to be influenced by the T migration of the TNM system, since the final pathological staging is impacted by the status of N in the case of ECE+ [20].

Finally, as already published, multivariate analysis confirmed a significant role of age in this specific group of patients [21,22].

Our study has some limitations such as its retrospective design, and some DOI values were reviewed retrospectively using an assumption concerning extrinsic muscle infiltration [15]. However, as far as we know, this is the first paper on a large cohort of patients uniformly affected by a specific subsite (mobile tongue cancer) that has investigated the performance of the 7th and the last two TNM editions (8th edition 2017-2020).

Conclusions

This study highlights how the new classification of the TNM (2020) more specifically defines prognosis of patients with OTSCC according to stage, increasing the risk of death and disease for the most advanced stages compared to previous staging systems (8th 2017 and 7th edition).

Further prospective evaluations are recommended to define the most accurate pre-operative methods to detect DOI and lymph node status, factors that determine the type of surgical resection and adjuvant therapies, and which influence prognosis.

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